PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/GB2004/001663	International filing date *(day/month/year)* 16.04.2004
Priority date *(day/month/year)* 16.04.2003	
International Patent Classification (IPC) or both national classification and IPC A61K31/565, A61K31/568, A61P9/00, A61P35/00, A61P11/06, A61P13/12	
Applicant MARGETTS, George	

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Allnutt, S Telephone No. +49 89 2399-7817

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/001663

JC20 Rec'd PCT/PTO 12 OCT 2005

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,2,3,7,12-21,29 and 30 (partially)

because:

☐ the said international application, or the said claims Nos. ---- relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,2,3,7,12-21,29 and 30 (partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,9-11,23-27
	No:	Claims	1-5,7,8,12-22,28-31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	6,9-11,23-27
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	29-31

2. Citations and explanations

see separate sheet

10/553111
JC20 Rec'd PCT/PTO 12 OCT 2005

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/001663

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 29-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. The term "angiotensin II related disease" used in claim 1 has no well-recognised meaning and leaves the reader in doubt as to which diseases/disorders are encompassed by this term, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

3. The application does not meet the requirements of Article 6 PCT, because claims 5 and 9 are not clear.
Claim 5 discloses cardiovascular diseases and includes diabetes and renal failure.
Claim 9 discloses proliferative diseases and includes peripheral arterial disease, cerebrovascular disease, cardiac myopathy, diabetic retinopathy, diabetic gangrene, diabetic nephropathy,scleroderma,aneurism and asthma.

4. The applicants attention is drawn to the fact that nephropathy is misspelt in claim 9 and atheroma is repeated.

5. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 2003/050291 A1 (ARAD YADON) 13 March 2003 (2003-03-13)
D2: GB-A-2 155 018 (STERWIN AG) 18 September 1985 (1985-09-18)
D3: SUZUKI GEORGE ET AL: "Effects of long-term monotherapy with eplerenone, a novel aldosterone blocker, on progression of left ventricular dysfunction and remodeling in dogs with heart failure." CIRCULATION, vol. 106, no. 23, 3 December 2002 (2002-12-03), pages 2967-2972, XP002288136 ISSN: 0009-7322
D4: YAMAKADO M ET AL: "Sites of action of beta-melanocyte stimulating hormone in aldosterone biosynthesis in the rat." PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE. SOCIETY

FOR EXPERIMENTAL BIOLOGY AND MEDICINE (NEW YORK, N. Y.) JUL 1985, vol. 179, no. 3, July 1985 (1985-07), pages 318-323, XP009033422 ISSN: 0037-9727

D5: ROCHA RICARDO ET AL: "Selective aldosterone blockade prevents angiotensin II/salt-induced vascular inflammation in the rat heart." ENDOCRINOLOGY, vol. 143, no. 12, December 2002 (2002-12), pages 4828-4836, XP002288137 ISSN: 0013-7227

D6: ROUSSEAU-MICHEL F ET AL: "Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: Results from the RALES neurohormonal substudy." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 40, no. 9, 6 November 2002 (2002-11-06), pages 1596-1601, XP002288138 ISSN: 0735-1097

D7: LEE A F ET AL: "Neurohormonal reactivation in heart failure patients on chronic ACE inhibitor therapy: a longitudinal study." EUROPEAN JOURNAL OF HEART FAILURE : JOURNAL OF THE WORKING GROUP ON HEART FAILURE OF THE EUROPEAN SOCIETY OF CARDIOLOGY. DEC 1999, vol. 1, no. 4, December 1999 (1999-12), pages 401-406, XP002288261 ISSN: 1388-9842

D8: EP-A-0 108 606 (STERWIN AG) 16 May 1984 (1984-05-16)

The documents considered in the present processing are consecutively numbered D1-D8; this numbering results from the citations D1-D8 found in the Search Report (SR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

6. The technical features of claims 1-5,7,12,13,18-21 and 29 are disclosed by document D1 and therefore does not fulfill the requirements of Art 33 (2) PCT with regard to novelty.

D1 discloses the use of 100-1000 mg/day of trilostane and epostane for treating insulin resistance and atherosclerosis.

7. The technical features of claims 1,2,7,8,12,13-22,28-31 are disclosed by document D2 and therefore does not fulfill the requirements of Art 33 (2) PCT with regard to novelty.
D2 discloses trilostane metabolites for treating breast and prostate carcinoma. Administration is preferably in particulate form at a unit dosage of 30-250 mg. The metabolites may be administered in combination with trilostane.

8. The remaining claims 6, 9-11, 23-27 are considered to be formally novel (Art 33(2) PCT).

Inventive Step

9. Claim 6 of the present application is not considered to involve an inventive step according to Article 33(3) PCT for the following reasons:
D1 already discloses the use of trilostane for the treatment of atherosclerosis and therefore the treatment of a further cardiovascular disease such as myocardial infarction would be an obvious step for the skilled person.

10. With respect to claims 9-11, the problem to be solved may be seen as "how to treat cardiofibrosis".
The solution as provided by the application is the use of steroid compound derivatives including epostane and ketostane.
D3 teaches that an aldosterone inhibitor may attenuate progressive intistitial fibrosis and thus improve heart failure.
D4 shows that WIN19578 blocks aldosterone production and therefore it would be obvious to the skilled person to select cyanoketone or a derivative thereof for solving the problem.
It is therefore noted, that the solution proposed in claims 9-11 of the present application is not considered not to satisfy the criterion set forth in Article 33(3) PCT.

11. The subject matter of claims 23-27 only involve the combination of compound of formula (I) and drugs already known to treat cardiovascular disorders (cf D5-D7). In particular D3 suggests that an ATII inhibitor and aldosterone inhibitor may attenuate progressive interstitial fibrosis and hence improve left ventricular diastolic function. Such a selection/combination can only be regarded as inventive, if the combination of compounds present unexpected effects or properties in relation to other ones. This does not appear to be the case and therefore claims 23-25,27 are not considered as

involving an inventive step (Art 33(3) PCT).

12. Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT). The applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, deletion or replacement, and to indicate the passages of the application as filed on which these amendments are based. Preferably, these indications should be submitted in hand written form on a copy of the relevant parts of the application as filed.

Further Remarks:

Industrial Applicability (Art 33(4) PCT).

13. For the assessment of the present claims 29-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.